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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,054	HERZOG ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *1-20 and 42-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *21-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/12/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/10/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Application, filed February 12, 2002, is a CIP of 09/308, 696, filed June 11, 1999, now abandoned, which is a 371 of PCT/AU98/00805 filed September 24, 1998, and claims priority to foreign application, PO9386, filed September 24, 1997, in Australia.

Claims 1-46 are pending.

Election/Restrictions

Applicant's election with traverse of Group V (claims 21-41) in the reply filed on December 9, 2004 is acknowledged. The traversal is on the ground(s) that there is no undue burden imposed on the Examiner in searching all sequences referenced in claims 21-41. Each of the sequences of SEQ ID NOs. 11-19 is derived from the full-length sequence or is a complementary sequence thereto. The nucleotide sequences are broadly related in structure either as SEQ ID NO. 1 or being derived from SEQ ID NO. 1 or its complementary sequence. SEQ ID NOs. 14-19 either are complements to teach other, or they share overlapping sequences. In short, a reasonable number of sequences (SEQ ID NOs. 14-17) would cover examination of SEQ ID NOs. 11-19. In addition to this, the Applicants direct the Examiner to the section "Examination of Patent Application Containing Nucleotide Sequences," which states that "up to ten (10) independent and distinct nucleotide sequences will be examined." This is not found persuasive. The Examiner took into consideration that these short sequences were to be used in an mRNA detection assay (either RT-PCR or in situ hybridization). The specification taught that these short sequences were specific for GPR56 and the short

sequences could thus be used to detect only GPR56 mRNA. However, a sequence search performed on SEQ ID NO. 14 demonstrated that SEQ ID NO. 14 could be found in nucleotide sequences encoding proteins other than GPR56. The fact that SEQ ID NO. 14 could be found in other nucleic acid sequences raised the issue that SEQ ID NOs. 15-17 could also hybridize to other nucleic acid sequences that do not encode GRP56. Searching the nucleic acid encoding GPR56 and the other nucleic acid sequences not encoding GPR56 comprised a search burden because searching for one could not be exclusive to another one. In response to the Applicants directing the Examiner of number of sequences to search, per the guidelines of "Examination of Patent Application Containing Nucleotide Sequences," the Examiner points out that the guidelines state that "nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to each other." It should be pointed out that the peptide sequences encoded by SEQ ID NOs. 11-19 are each unique and distinct. Furthermore, the guidelines also state that "up to 10 independent and distinct nucleotide sequences will be examined." One sequence is considered "up to" 10.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-20, 42-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 9, 2004.

Claims 21-41, drawn to a diagnostic method of determining the level of GPR56 mRNA in a test sample and SEQ ID NO. 14 are under consideration.

Specification

The specification states that SEQ ID NO. 11-19 would be provided in Table 1 (see page 59, line 20). However, no Table 1 was found in the specification or drawings.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is a method of detecting the presence of GPR56 on cancer cells and effector memory T cells.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

With regards to <u>any</u> method of detecting GPR56 mRNA, the art teaches that there are two major methods: RT-PCR and in situ hybridization (on tissue samples and Northern blots). While the specification teaches that 20-30-mer primers specific for GPR56 were generated (page 58, lines 21-24), the specification does not teach what combination of forward and reverse primers should be used in a PCR reaction. The response to the election has pointed out that SEQ ID NO. 14 and SEQ ID NO. 11 were complementary sequences derived from nucleotides 327 to 348 of SEQ ID NO. 1 (page 3, lines 1-2), however, primers made from SEQ ID NO. 14 and SEQ ID NO. 11 would not generate any PCR product. Similarly, if one were to use primers comprising SEQ ID NO. 19 and SEQ ID NO. 14 in the PCR reaction, no PCR product would form. The specification provides no guidance on how to use any combination of primers taught in SEQ ID NOs. 11-19 in a PCR reaction. In addition to this, the sequences of SEQ ID

NOs. 11-19 could be used in a Northern blot or an in situ hybridization of a tissue. While sense probes cannot be used in an in situ (thus eliminating SEQ ID NO. 11-13), the specification states that the generated probes to regions within the entire sequence that were not present in other gene other than human GPR56-encoding genes, a search of SEQ ID NO. 14 has demonstrate that SEQ ID NO. 14 also hybridizes to a human secreted protein (see sequence search results, us-10-073-054-14.rng, page 5, second col.). Thus, the specification does not provide guidance to the skilled artisan how to use SEQ ID NO. 14 in an in situ hybridization assay and discriminate a nucleotide sequence encoding secreted protein from a nucleotide sequence encoding GPR56. With regards to using SEQ ID NO. 1 (the nucleotide sequence encoding full length GPR56), a skilled artisan could use this nucleic acid sequence as a probe in a Northern blot or an in situ hybridization to detect expression of GPR56 mRNA. For the reasons described above, the specification only enables a skilled artisan to detect GPR56 mRNA by in situ hybridization (Northern blot or by whole mount tissue/cells) using SEQ ID NO. 1.

While the art has shown that detecting levels of mRNA in a cell or tissue sample is a common way of identifying a cell or tissue sample, the instant specification does not teach a skilled artisan how to use the mRNA of GPR56 as an indicator of disease or inflammation mediated by T cells. The specification provides correlative data that the expression of GPR56 might indicate disease (cancer) or that a T cell is an effector memory cell. However, the specification does not provide ways for a skilled artisan to discriminate cancer from healthy tissue and cancer from a T cell mediated infection, such that a skilled artisan could determine the presence of any effector memory T cell

response from cancer and from re-infection with an infectious agent. The specification also does not teach how to determine the presence of effector memory T cells from any other cell in a test sample.

With regards to a method of detecting any cancer cell, the specification teaches that the nucleic acid sequence encoding GPR56 was detected in the ovary or omentum of early stage or advanced ovarian cancer patients and in the prostate of cancer patients. While the specification teaches these two embodiments, it does not teach a skilled artisan that the expression of the nucleic acid sequence encoding GPR56 is a common characteristic of all cancers, nor does the specification teach a skilled artisan the correlation between the higher expression of nucleic acid sequence encoding GPR56 and any cancer cell. For this reason, the specification does not teach a skilled artisan to practice the claimed invention on all types of cancer.

With regards to a method for detecting ovarian or metastases in omentum tissue in a subject, the specification teaches that a hybridization assay was used to detect nucleic acid sequences that encode human GPR56 in ovary and omentum samples of cancer and patients and from ovary samples of normal patients. Figure 2 is a graphical representation of the hybridization showing relative expression of the nucleic acid encoding human GPR56 (see Brief Description of the Drawings, pages 15-16). The graph illustrates 6 patients (columns 1-6) had borderline ovarian cancer, 34 patients (columns 7-44) had ovarian cancer, 11 patients had ovarian cancer and metastases or secondary cancers of the omentum (columns 45-55); control tissue was obtained from 5 patients who had no ovarian cancer (columns 56-59) and 1 patient who had no

omentum cancer (column 60). The specification teaches that there was a 6-7 fold enhancement of GPR56 expression in early and advanced cancers of the ovary and/or metastases of the omentum (page 16, lines 12-14). While it could be contemplated that a 6-7 fold enhancement of GPR56 expression could be indicative of ovarian cancer, the specification does not teach that cancer tissue expresses 6-7 fold more GPR56 mRNA. For example, patient 6's ovary expresses a relative level of 225. Normal patient 59's ovary expresses a level of 90. A level of 225 is not 6-7 fold more than 90. Similarly, patient 41's ovary expresses a relative level of 289. Patient 58's ovary expresses a relative level of 66. A level of 289 is not 6-7 fold more than 66. These results suggest that using the fold-levels of mRNA expression of GPR56 is not a reliable way of determining whether a patient has ovarian cancer. Similarly, with regards to using fold levels to determine whether a patient has metastatic cancer in the omentum, patient 51's omentum has a relative level of 280, while patient 60's omentum is 192. A level of 280 is not 6-7 fold over that of 192. For this reason, using the fold-levels of mRNA expression of GPR56 is not a reliable way of determining whether a patient has cancer in the omentum. While one may argue that there is variability between patients, the specification has not taught how to normalize the results so that the levels of GPR56 mRNA could be compared. One may also argue that variability may occur because patients have additional GPR56 mRNA-upregulated expression events, such as a bacterial infection. If that is the case, the specification has not taught how to measure levels of GPR56 mRNA in cancer cells in a patient that has cancer and an otherwise "normal" patient with a bacterial infection. The specification teaches that similarly, high

levels of expression were observed in subjects having prostate cancer (page 62, lines 28-29). However, since the specification did not teach a reliable way to detect cancer (i.e. that ovarian cancer cells expressed GPR56 mRNA at a level 6-7 times more than ovarian cells of a healthy patient) a skilled artisan cannot predict that there would be a 6-7 fold increase of GPR56 mRNA levels of prostate cancer tissue versus normal prostate tissue.

With regards to a method for determining any effector memory T cell response, the art teaches that CCR- memory cells express receptors for migration to inflamed tissues and display immediate effector function (Sallusto, et al. 1999, Nature, 401: 708-712, see abstract, page 708, line 12 to page 709, line 1). While the specification teaches a method determining levels of GPR56 mRNA, the specification does not teach any parameters of what is considered to be a T cell response. The specification does not teach any method of how effector memory T cell response is monitored, such as how skilled artisan would monitor migration of CCR- cells to inflamed tissue, and how a skilled artisan would monitor effector function, e.g. cytokine release. A skilled artisan would need guidance as to how to discriminate effector memory T cells from other types of T cells, and T cells from metastatic cancer cells in the biopsied tissue.

With regards to a method for determining if a subject has been re-infected with any infectious agent, the art teaches that CCR7+ memory cells express lymph-node homing receptors and lack immediate effector function, but efficiently stimulate dendritic cells and differentiate into CCR7- effector cells upon secondary stimulation (Sallusto et al., abstract, page 709, lines 1-4). This means that to determine "re-infection," a skilled

artisan would need be taught a method of monitoring the transition of CCR7+ cells to CCR7- cells. In addition to this, with respect to the word "re-infection," the use of the "re-" prefix implies that a skilled artisan knows what infection is being monitored and that the skilled artisan knows that this is not the first exposure to the pathogen. However, the specification has not taught a skilled artisan the steps needed to determine what infection is being monitored and how to determine whether the infection at hand is the patient's first.

With regards to determining the presence of effector memory T cells in a test sample, the specification teaches the correlative data that effector memory T cells express GPR56 mRNA. However, the specification does not teach how to discriminate effector memory T cells from any population of cells. A skilled artisan cannot assume that because a cell expresses GPR56 mRNA that it is an effector memory T cell because the specification also teaches that metastatic cancer cells express GPR56 mRNA. In addition to this, the method encompasses a process for counting effector memory T cells in a subject (claim 41). This method comprises normalizing the hybridization signal to determine T cell count. However, the specification does not teach how to select the reference point and how to normal the hybridization signals to that reference point. For this reason, the specification has not enabled a skilled artisan to determine the presence of effector memory T cells in a test sample. The specification also has not enabled a skilled artisan to normalize a hybridization signal in a process to count effector memory T cells in a subject.

In view of the lack of guidance, working examples, breadth of the claims, of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 25, 35, 37 use the phrase, "comparable sample from a healthy or normal individual," however, the metes and bounds of what is considered "healthy" or "normal" is unclear because these are relative terms.

Claim 24 is awkwardly written. Claim 24 is to a method wherein the samples comprise cells derived from a tissue. The list includes blood, urine, semen, abdominal fluid, serum, a cell preparation or nucleic acid preparation derived therefrom. None of these are cells derived from tissue. Also, a "nucleic acid preparation derived therefrom," is not a cell.

Claims 26, 38 use the phrase, "at least low stringency hybridization conditions." "Low stringency" is a relative term and the metes and bounds of what is considered "low" are unclear.

Claim 39 is unclear. According to the Merriam-Webster online dictionary, blood serum is "*noun*: blood from which the fibrin and suspended material (as cells) have

been removed." Thus, a test sample cannot comprise whole serum or a fraction thereof comprising T-cells.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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